Title: EASD 23: Efinopegdutide in NAFLD & Type 2 Diabetes Patients
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Dr Samuel S Engel:
Hi, I'm Dr. Sam Engel. I am in the Global Clinical Development Group at Merck Research Laboratories, and the title of my presentation is "The Efficacy and Safety of Efinopegdutide in Patients with Nonalcoholic Fatty Liver Disease and Type 2 Diabetes, Results from an Active Comparative Controlled Study."

What is the unmet need in this patient population?

For patients who have what you know had been referred to as NASH or nonalcoholic steatohepatitis. More recently, the nomenclature is changing to call it metabolic associated steatohepatitis or steatotic liver disease. There are currently no available therapies, and so NASH or MASH as some call it, is a leading cause of liver transplant and other complications related to end-stage liver disease. With no effective therapies available, there's clearly a very high unmet medical need for us to address this problem.

What is the mechanism of action of the study drug?

Efinopegdutide is a dual agonist of the GLP1 and glucagon receptors. We believe that dual agonism offers a particular benefit in terms of reducing liver fat, since we can leverage both the weight loss effects that are observed with GLP1-based therapies as well as the complementary effects of glucagon on weight loss, but also importantly, the direct effects of glucagon on hepatic fat metabolism.

What is the study design and patient population?

Overall study included patients both with diabetes and without diabetes. This was an active, comparator-controlled study. We used efinopegdutide at a dose of 10 milligrams, reached with three titration steps compared to semaglutide 1 milligram, also reached with three titration steps. At the time the study was designed, higher doses of semaglutide were not available. Patients titrated the drugs over the course of 8 weeks and then continued therapy for a total of 24 weeks. Liver fat was measured both at baseline and at the 24-week time point using the MRI PDFF technique, which is the gold standard for measuring liver fat population.
So, as I mentioned, the overall population included patients both with diabetes and without diabetes. For the purpose of the presentation that we've presented at the EASD meeting, we've done a subgroup analysis looking at the efficacy and safety of both drugs in the study, in the type two diabetes cohort, which represented about 30% of the population and in the nondiabetes cohort.

What are the key results?

So overall, as we had previously reported, there was a substantial reduction in liver fat with efinopegdutide, approximately a 73% relative reduction in liver fat, compared to approximately 42% with semaglutide one milligram.
n this study, this post hoc analysis, we also looked at the two subgroups, the diabetes and the nondiabetes subgroups, and the reductions in liver fat were similar for both drugs in both the diabetes and the nondiabetes subgroups, some minor differences which we described in the presentation. Importantly, we looked also not just at the relative reduction in liver fat, but we performed responder analyses which assessed how many patients achieved certain thresholds of liver fat reduction. For example, a 30% reduction in liver fat is thought to be necessary for histologic benefit.
We also looked at other thresholds of liver fat reduction, including what we would call super responders, those people who had at least 70% reduction in liver fat. And there we saw very minimal differences between the diabetes and the nondiabetes subgroup.
This is important because given that the dual agonist contains substantial glucagon activity and because of the known effects of glucagon on impacting glucose metabolism, we needed to understand whether or not there would be any negative effects of glucagon agonism on liver fat metabolism in the diabetes supplement.

What are the take-home messages for practice?

I think the take-home messages for practitioners are really that when we think about new therapies for NASH, we need to also understand how they behave in specific patient subgroups. Obviously for this presentation, we focused on a diabetes subgroup, but there are potentially differences in other baseline characteristics.
There are differences, for example, in different ethnic groups in terms of the way that NASH evolves. For example, the Hispanic population has a higher prevalence of NASH and also, even given the same level of disease, they tend to carry more of a burden in terms of the complications. And so, the take-home message from my point of view is as we start to consider therapies for the broad category of patients, we also do need to focus in on specific subgroups that may or may not differ in their response to a given therapeutic.

What are the next steps?

For efinopegdutide, we have moved on to a phase IIb study which is currently underway. This is a study that will look at histologic endpoints using a liver biopsy at baseline after one year of treatment. This is both a placebo and active controlled study. The active control is semaglutide 2.4 milligrams. We have three different doses of efinopegdutide and a placebo group. And we think this will be the next step in terms of understanding whether these substantial benefits in terms of liver fat reduction translate similarly into benefits on histology.